# Consideration of Endocrine-Mediated Mode of Action and Life-Stage Specific Susceptibility in the Risk Assessments for Two Pesticides

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## Background

ORD has historically contributed to the risk assessments of specific individual pesticides or classes of pesticides through:

- Test methods development
- Generation of data
- Consultation with the Office of Pesticide Programs (OPP).

# **Atrazine and Vinclozolin**

- Atrazine and vinclozolin are widely used pesticides
- OPP was conducting re-registration evaluations under FIFRA (the Federal Insecticide, Fungicide, and Rodenticide Act)
- Required an assessment of potential risks to children, as mandated by FQPA (the Food Quality Protection Act).

## **ORD Research and Consultation**

- ORD research focused on:
  - Characterizing the mode of action (MoA)
  - Determining the effects of exposure across varying life stages (e.g., prenatal, postnatal, peri-pubertal, and adult).
- Extensive collaboration and consultation between ORD and OPP occurred while developing the risk assessments.

Wolf et al., 1999

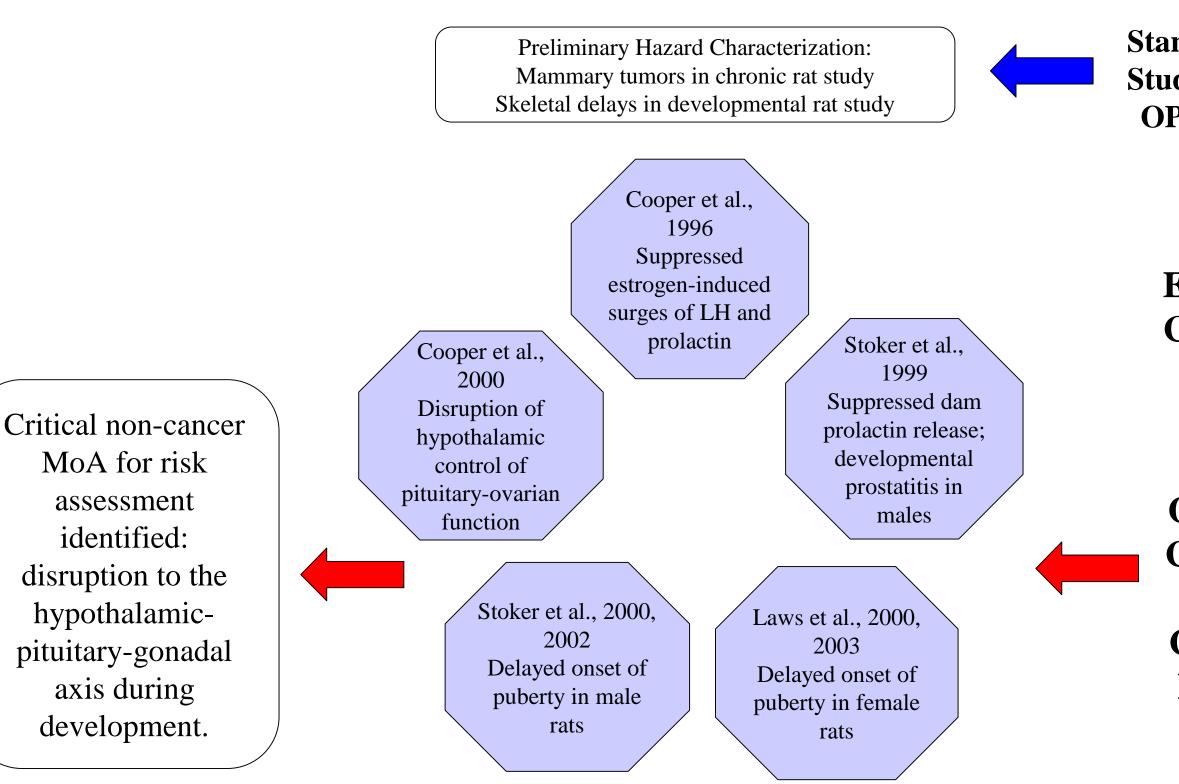
Reproductive

malformations in

male rat

male rat

### Methods/Approach



**Standard Toxicology** Preliminary Hazard Characterization: **Studies Submitted to** Hypospadias in two-generation reproduction study Histopathology in chronic rat study **OPP** by Registrant Ostby et al., 1999 Altered sexual **Endocrine** differentiation in male rat **Concerns** Monosson et al 1999 Delayed puberty; inhibited develop. of androgendependant tissues **ORD Studies** Conducted to **Further** Gray et al., 2001 Gray et al., 1999 Multiple Characterize Altered sexual reproductive differentiation in Hazard and malformations in male rat **Dose** 

Response

**OPP** 

Risk

**Assessment** 

The anti-androgenic MoA was characterized, and the dose-response profile was identified for critical developmental and reproductive effects

related to this MoA.

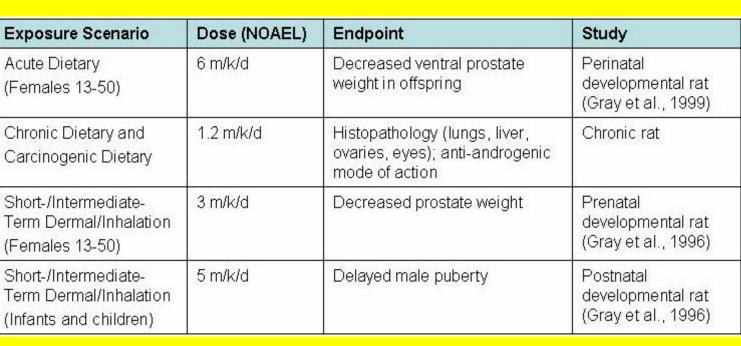


Atrazine – Interim Reregistration Eligibility Decision (2003)

Exposure Scenario	Dose (NOAEL)	Endpoint	Study
Acute Dietary Females 13-50	10 m/k/d	Delayed ossification (NOAEL supported by prostatitis in male offspring, Stoker et al., 1999)	Developmental rat and rabbit
Chronic Dietary	1.8 m/k/d	Attenuated LH surge as biomarker for hypothalamic disruption	6-mo LH surge
Short-term Dermal/Inhalation	6.25 m/k/d	Delayed preputial separation	Pubertal assay (Stoker et al., 2000)
Intermediate-Term Dermal/Inhalation	1.8 m/k/d	Attenuated LH surge as biomarker for hypothalamic disruption	6-mo LH surge

Public perception of potential risks was refocused away from cancer and onto neuroendocrine-mediated reproductive/developmental risks to susceptible populations.

# Vinclozolin - Reregistration Eligibility Decision (2000)



Risk Mitigation/ Risk **Communication** 

Cancellation and/or limitation of specific uses to reduce potential exposures to children

### **ORD's Contribution to OPP's Risk Assessment**

- Research conducted or supported by ORD to fill specific, critical data gaps, contributed to the characterization of MoA amd life-stage specific susceptibility issues.
- For both atrazine and vinclozolin, ORD studies provided:
  - Methodologies to assess hazard
  - Confirmation of susceptibility during specific life stages
  - Support for decisions regarding the adverse consequences of the observed effects
  - A basis for extrapolation from animal data to potential human response. Information critical in identifying the point of departure for risk assessments conducted by OPP.

### **Outcome and Impact**

OPP's risk management decisions addressed the protection of susceptible populations, in relation to the critical endocrine-mediated mode of action.

- **<u>Atrazine:</u>** Risk communication efforts were critical in refocusing public perception of potential risks, away from long-term cancer concerns (the focus of past risk assessments) and towards non-cancer endocrine-mediated risks to susceptible populations.
- Vinclozolin: Data generated by ORD were utilized in establishing endpoints and doses for short- and intermediate-term non-dietary risk assessments and for characterizing remaining data gaps and uncertainties. Characterization of risks associated with vinclozolin exposures during development resulted in risk mitigation actions (cancellation and/or limitation of specific uses to reduce potential exposures to children).

### **Atrazine References:**

Cooper, R.L. et al. (1996) Reprod. Toxicol. 10(4):257-264. Stoker, T.E. et al. (1999) Toxicological Sciences 52(1):68-79. Cooper, R.L. et al. (2000) Toxicological Sciences 53:297-307 Stoker, T.E. et al. (2000) Toxicological Sciences 58:50-59. Laws, S.C. et al. (2000) Toxicological Sciences 58(2):366-76. Stoker, T.E. et al. (2002) Toxicological Sciences 67(2):198-206 Laws S.C. et al. (2003) Toxicological Sciences 76(1):190-200. USEPA (2003) Atrazine IRED (http://cfpub.epa.gov/oppref/rereg/status.cfm?show=rereg)

### **Vinclozolin References:**

Gray Jr., L.E. (1996) Presentation to FIFRA SAP. Gray Jr., L.E. et al. (1999) Tox. Indust. Health 15(1-2):48-64. Monosson, E. et al. (1999) Tox. Indust. Health 15:65-79. Ostby, J. et al. (1999) Tox. Indust. Health 15:80-93. Wolf, C. et al. (1999) Tox. Indust. Health 15:94-118. USEPA (2000) Vinclozolin RED

(http://cfpub.epa.gov/oppref/rereg/status.cfm?show=rereg)



